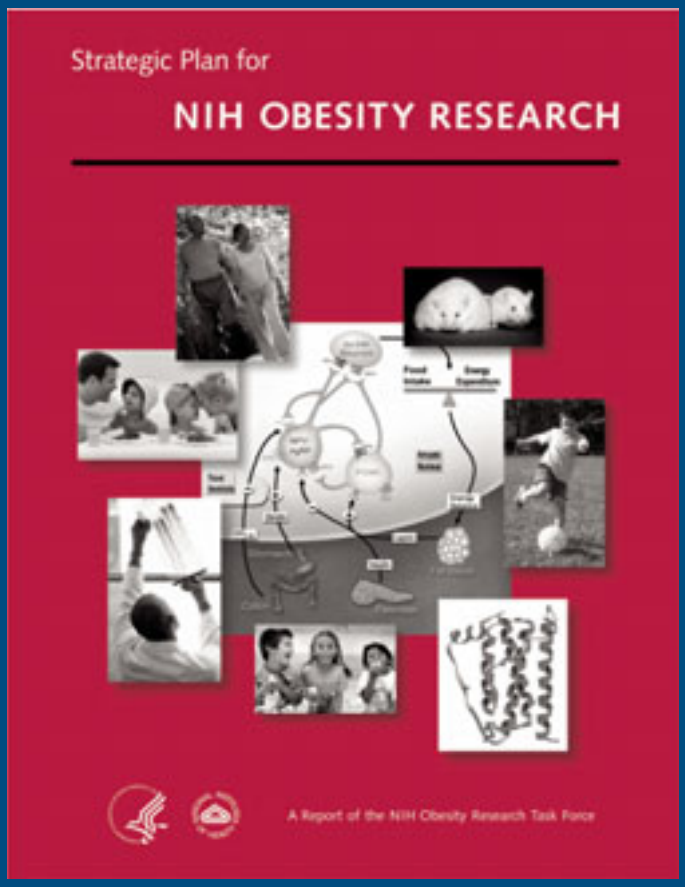

The *Strategic Plan for NIH Obesity Research*, published in August 2004, is intended to serve as a guide for coordinating obesity research activities across the NIH and for enhancing the development of new efforts based on identification of areas of greatest scientific opportunity and challenge. It was developed by the NIH Obesity Research Task Force with critical input from external scientists and the public. The *Strategic Plan* is posted on the Task Force's Website, *http://obesityresearch.nih.gov/index.htm*. The Website also lists current NIH obesity research funding opportunities for investigators, and links to NIH health information Websites for the public and healthcare professionals.

Obesity

Obesity has risen to epidemic levels in the U.S. Obese individuals suffer devastating health problems, face reduced life expectancy, and experience stigma and discrimination. A strong risk factor for type 2 diabetes, obesity is also associated with other health conditions within the NIDDK's mission, including, for example, urinary incontinence, gallbladder disease, and the fatty liver disease non-alcoholic steatohepatitis.

Nearly 31 percent of U.S. adults are considered obese based on body mass index (BMI), a measure of weight relative to height.[1] Furthermore, while obesity and overweight have risen in the population in general, the greatest increases observed over approximately the past two decades have been in the prevalence of extreme obesity; those who are severely obese are most at risk for serious health problems.[2] Levels of childhood overweight have also escalated in the past several decades; approximately 16 percent of children and teens ages 6 through 19 are now overweight.[1,3] The levels of pediatric overweight have ominous implications for the development of serious diseases both during youth and later in adulthood. Overweight and obesity also disproportionately affect racial and ethnic minority populations, and those of lower socioeconomic status.

The increased prevalence of obesity in the U.S. is thought to result from the interaction of genetic susceptibility with behavior and factors in the environment that promote increased caloric intake and sedentary lifestyles. Thus, the NIDDK has been supporting a multidimensional research portfolio on obesity ranging from basic studies to large clinical trials. This research includes, for example, investigations to elucidate the hormones and signaling pathways that influence appetite and energy expenditure; exploration of genetic factors that predispose individuals to obesity; studies of nutrition, including diet composition; research encompassing physical activity; and studies aimed toward obesity prevention through the development and testing of modifications of environmental factors in schools, the home, and other settings. The NIDDK additionally supports research on eating disorders that are associated with obesity in some people. Highlights of recent advances from NIDDK-supported research on obesity are provided in this chapter. To help bring the results of research to the public and health care providers, the NIDDK also sponsors education and information programs.

Given the importance of the obesity epidemic as a public health problem, and its relevance to the mission of the NIDDK, the Institute has played a leading role in the NIH Obesity Research Task Force. Established by the NIH Director and co-chaired by the Directors of the NIDDK and the National Heart, Lung, and Blood Institute, the Task Force also includes representatives from numerous other NIH Institutes, Centers, and Offices. A major effort of the Task Force has been the development, with extensive input from external scientists and the public, of the *Strategic Plan for NIH Obesity Research*, published in August 2004 (*http://obesityresearch.nih.gov/About/strategic-plan.htm*).

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[1] Statistics Related to Overweight and Obesity. NIH Publication No. 03-4158, July 2003. *http://win.niddk.nih.gov/statistics/index.htm*; Hedley et al. 2004. *JAMA* 291: 2847-50.

[2] Flegal et al. 2002. *JAMA* 288: 1723-7; Flegal and Troiano. 2000. *Int. J. Obes Relat Metab Disord* 24: 807-18; Freedman et al. 2002. *JAMA* 288:1758-61.

[3] This document uses the terms overweight and obesity interchangeably for children and adolescents because there is no generally accepted definition for obesity, as distinct from overweight, in this age group.

STRATEGIC PLAN FOR NIH OBESITY RESEARCH

The *Strategic Plan* is intended to serve as a guide for coordinating obesity research activities across the NIH and for enhancing the development of new efforts based on identification of areas of greatest scientific opportunity and challenge. The *Strategic Plan* seeks to maximize collaboration among the NIH components and to capitalize on their expertise and interest in developing obesity research initiatives.

Reflecting a dynamic, trans-NIH planning process, the *Strategic Plan* presents a multi-dimensional research agenda, with an interrelated set of short-, intermediate- and long-term research goals, and strategies for achieving the goals. It builds upon a foundation of knowledge from past NIH-supported scientific advances. These advances range from the discovery of the hormone leptin, which ignited the field of molecular research into appetite control and body weight regulation, to the results of behavioral studies that led to the success of the Diabetes Prevention Program, a clinical trial demonstrating that moderate weight loss and exercise can dramatically reduce the risk of type 2 diabetes in persons at high risk for development of this disease. The major scientific research themes around which the *Strategic Plan* is framed include the following:

- Preventing and treating obesity through lifestyle modification;
- Preventing and treating obesity through pharmacologic, surgical, or other medical approaches;
- Breaking the link between obesity and its associated health conditions—including type 2 diabetes, heart disease, certain cancers, and many other health conditions;
- Cross-cutting topics, including health disparities, technology, fostering of interdisciplinary research teams to bridge the study of behavioral and environmental aspects of obesity and the study of genetic/biologic factors, investigator training, translational research, and education/outreach efforts.

Through the efforts described in the *Strategic Plan for NIH Obesity Research*, the NIH will strive to bolster progress in obesity research to improve public health.

Highlights of New NIDDK Obesity Research Initiatives: The NIDDK is pursuing a range of research avenues that will help meet the goals of the *Strategic Plan*. Critical among these is vigorous support of investigator-initiated research projects. Following are examples of efforts initiated by the Institute, in consultation with the external scientific and lay communities.

Basic Research

Several efforts will advance the understanding of the fundamental biological processes that lead to obesity. For example, the NIDDK is spearheading the development of an initiative to further understand the neurobiological basis of obesity. The NIDDK has launched an effort to bolster genetic studies of obesity-related traits in model organisms, and is planning a future endeavor to accelerate the search for obesity-related genes from human samples. The Institute is also developing a new initiative to enhance mechanistic studies of the impact of the intrauterine and neonatal environment on obesity and diabetes in offspring. Examples of research activities in other areas include the NIDDK's collaboration on an NHLBI-led initiative on bioengineering approaches to energy balance and obesity, and NIDDK's participation in an effort, led by the National Cancer Institute, to advance research on the economics of diet, activity, and energy balance.

Bridging Basic and Clinical Research

The NIDDK is pursuing a multipronged approach to promoting partnerships between basic and clinical researchers in obesity in order to propel new scientific advances. Two recent initiatives are capitalizing on major ongoing NIH research investments by soliciting ancillary studies to several existing obesity-related clinical trials and networks. A third effort independently encourages productive partnerships between basic and clinical researchers.

For the efforts focused on ancillary studies, NIDDK trials and networks that would accept meritorious obesity-related ancillary studies include:

- *Look AHEAD (Action for Health in Diabetes)*, a multi-site clinical trial which will examine the health effects of an intervention to achieve and maintain long term weight loss, through physical activity and decreased caloric intake, in 5,000 obese adults with type 2 diabetes;
- *Diabetes Prevention Program Outcome Study (DPPOS)*, described in this document in the chapter on diabetes, endocrinology, and metabolic diseases;
- *Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY)* study, described in this document in the chapter on diabetes, endocrinology, and metabolic diseases;
- *NASH (nonalcoholic steatohepatitis) Clinical Research Network*, established to study this liver disease, which is associated with obesity;
- *Longitudinal Assessment of Bariatric Surgery (LABS)* clinical research consortium;
- *Program to Reduce Incontinence by Diet and Exercise (PRIDE)*, which will examine the impact of weight loss on urinary incontinence in overweight and obese women.

Another trial that would accept ancillary studies is sponsored by the National Institute on Aging and focuses on caloric restriction.

The NIDDK is pursuing research on long-term weight maintenance through a solicitation to encourage both basic and clinical studies in this area. With another new effort, the NIDDK is encouraging research on diet composition and energy balance to understand how different aspects of foods affect food intake, energy expenditure, and weight change.

Childhood Obesity

To bolster research on the urgent health problem of childhood obesity, the NIDDK is encouraging new studies to explore site-specific strategies for preventing and treating childhood obesity, as part of the efforts of the NIH Obesity Research Task Force. Sites encompassed by this initiative, for which meritorious research projects would be supported, include the family/home, day-care or pre-school, school, or other appropriate community venues. A complementary Task Force initiative encourages research to prevent or treat obesity in primary care settings.

New NIH Obesity Research Website: The NIDDK led the efforts of the NIH Obesity Research Task Force to develop a new obesity research Website, which was launched last year; the URL is *http://obesityresearch.nih.gov*. The primary purposes of this Website are to help inform investigators about current NIH funding opportunities for obesity research, to provide information on NIH-sponsored scientific meetings relevant to obesity, and to provide other information relevant to obesity research. In providing this information, the Website will reflect the dynamic and ongoing planning process for obesity research at the NIH. *The Strategic Plan for NIH Obesity Research* is also posted on the site. Finally, although the focus of the Website is on research, the site also includes links to other NIH Websites that provide information to the public and health professionals on weight loss, nutrition, physical activity, and health problems associated with obesity.

RESEARCH ADVANCES

Recent NIDDK-supported advances in research on obesity range from basic studies of the brain, fat tissue, and gut; to a study of teens and fast food; to assessments of potential intervention approaches.

Appetite-suppressing Hormone Rewires Brain Circuitry: The hormone leptin suppresses food intake and helps regulate body weight by communicating signals from fat cells to a part of the brain known as the arcuate nucleus of the hypothalamus (ARH). Recent studies have now shown that leptin is also fundamentally involved in developing the neural circuits in the brain that control feeding. The studies compared normal mice with mutants that are obese because they cannot produce leptin.

Distant brain cells communicate with each other by relaying electrical messages via long, wire-like connections called axons. In leptin-deficient mutant mice, the density of axons growing from the ARH was low, suggesting that one of the roles for leptin in normal mice is to promote axon outgrowth. In support of this, treating juvenile mutant mice with leptin during a critical window of time in their development restored normal patterns of brain growth. In another study, researchers found a method of distinguishing between the brain cells that control hunger and those that control satiety in a way that would permit assessment of leptin's effects on axons reaching these cells from elsewhere in the brain. Leptin-deficient mice exhibited an imbalance in physical and electrical input connections of these populations of leptin-sensitive cells. However, after just six hours of leptin treatment, the brains in the mutant mice were able to rewire and form new connections; these changes in the brain preceded observed changes in feeding behavior. Taken together, these studies mark the beginning of new and exciting advances that merge obesity research with neurobiology to demonstrate a new role for leptin in controlling the body's energy balance by regulating both long-term connections and dynamic changes in the brain.

Pinto S, Roseberry AG, Liu H, Diano S, Shanabrough M, Cai X, Friedman JM, and Horvath TL. Rapid rewiring of arcuate nucleus feeding circuits by leptin. *Science* 304: 110-115, 2004.

Bouret SG, Draper SJ, and Simerly RB. Trophic action of leptin on hypothalamic neurons that regulate feeding. *Science* 304: 108-110, 2004.

Cells of the Immune System Accumulate in the Fat Tissue of People Who Are Overweight: More than 65 percent of U.S. adults are overweight or obese, with nearly 31 percent of adults—over 61 million people—meeting criteria for obesity. Some studies have found that obese and overweight individuals have elevated levels of certain compounds in the blood that are typically observed in cases of chronic, low-grade inflammation. However it has been unclear whether these compounds result from inflammation of a single discrete part of the body, or whether they are system-wide in origin. In any case, a better understanding of obesity-related inflammation may be valuable for improving treatment for overweight patients. Using DNA microarray technology that allowed them to probe a vast array of genomic elements, researchers recently identified genes that are turned on at higher levels in fat tissue of obese mice, as compared to lean mice. Many of these genes turned out to be those that are turned on in macrophages, which are cells that contribute to the immune response, in part by inducing inflammation. Indeed, they next observed that the number of macrophages in fat tissue increased in proportion to the weight of the mouse. When they examined cells from samples of fat tissue in humans, they found a similar correlation: about 10 percent of the cells in fat samples from lean people were identified as macrophages, whereas 40 percent of the cells were macrophages in fat samples obtained from severely obese subjects. These results suggest that the cellular functions of macrophages in fat tissue may play a role in obesity and its associated disorders, and may be important therapeutic targets as well.

Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, and Ferrante Jr, AW. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 112: 1796-1808, 2003.

Statistical references: Statistics related to overweight and obesity. NIH Publication No. 03-4158, 2003. (*http://win.niddk.nih.gov/statistics/index.htm*); Hedley et al. JAMA 291: 2847-2850, 2004.

Gut Bacteria and Fat Storage: While some researchers are elucidating the complex network of hormones that control appetite and energy expenditure, and others are investigating behavioral and environmental factors that promote excess calorie consumption and sedentary lifestyles, one group of scientists is pursuing quite a different area of research toward increased understanding of obesity—gut bacteria. An enormous number of microorganisms normally reside in the gut.

Collectively referred to as the gut microbiota, these bacteria do not cause disease as would, for example, food-borne pathogens; rather, they exist relatively peacefully, and help digest various foods that their "host" human (or animal) would otherwise not be able to digest. In experiments comparing conventionally-raised mice to those raised in special laboratory conditions without microorganisms (germ-free), the scientists discovered that conventionally-raised mice contain more body fat than their germ-free counterparts. When previously germ-free mice were given gut microorganisms, they dramatically increased their total body fat content—even while decreasing their food consumption. The scientists then found that the mice also developed insulin resistance, a condition often associated with obesity and that can lead to the development of type 2 diabetes. In experiments designed to uncover the molecular mechanism for this fat storage, the scientists learned that the gut microbiota can increase the uptake of certain sugars from the gut, hence increasing the amount of calories harvested from the diet, and can boost the production of liver enzymes involved in fat production. Further, they found that in germ-free mice, a protein called Fiaf is induced; Fiaf reduces the storage of fats in fat cells. Gut microbiota suppress Fiaf, however, consequently increasing fat storage. From these studies, the scientists suggested that the gut microbiota is an important "environmental" factor that influences dietary energy acquisition and fat storage, and that increasing Fiaf activity may promote leanness.

Backhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, and Gordon JI. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci USA* 101: 15718-15723, 2004.

Teens, Fast Food, and Obesity: As more children and adolescents have become overweight in the past several decades, one often-cited contributing factor is "fast food." Yet, while some teens who regularly eat fast food are overweight, others remain lean. In a study to try to understand why, investigators observed that lean adolescents—unlike those who were overweight—seemed to compensate for fast-food calorie intake. That is, the total amount of calories (or energy) the lean adolescents reported consuming on days when they ate fast food was not different from their caloric intake on days when they ate other types of food. In the first part of this study, the researchers offered a fast food meal, in a food court, to 54 teen participants who were age 13 to 17 years and who normally ate at least one fast food meal per week. The food available to the teens consisted of typical fast food fare, and the investigators provided as much food as each participant wanted. Both the overweight and lean adolescents overate, consuming far more calories in one meal than would be necessary for their energy needs, given that they would also be eating other meals on that day. Furthermore, the overweight participants consumed more calories than those who were lean. In the second part of the study, the researchers interviewed the teens on each of several days to ask about their diet on the preceding day. Based on what the study participant had eaten, the researchers then classified those days as either "fast food days" or "non-fast food days." The overweight teens reported consuming significantly more calories on fast food days than on non-fast food days. Although it is not clear whether such eating patterns were a cause of overweight or were secondary to weight gain, the researchers suggest that fast food consumption may at least help maintain or exacerbate obesity in susceptible individuals. By contrast, the lean study participants reported consuming a similar amount of calories on both types of day. Thus, the researchers concluded that the lean adolescents may be compensating, in their overall eating habits, for the excess calories of a typical fast food meal. The researchers cautioned, however, that effects of fast food on diet quality would suggest that such food may not be without potential detrimental effects in lean adolescents.

Ebbeling CB, Sinclair KB, Pereira MA, Garcia-Lago E, Feldman HA, and Ludwig DS. Compensation for energy intake from fast food among overweight and lean adolescents. *JAMA* 291: 2828-2833, 2004.

Liposuction Does Not Improve Risk Factors for Diabetes and Coronary Heart Disease: Liposuction is a common surgical procedure that removes substantial amounts of fat from specific areas of the body including the abdomen, hips, and thighs. Researchers have now demonstrated that liposuction to decrease fat mass in obese individuals is not an effective approach to reduce risk factors for developing serious diseases associated with obesity such as type 2 diabetes and coronary heart disease. In a study of 15 obese women, seven of whom had type 2 diabetes, researchers evaluated key obesity-associated risk factors for heart disease and diabetes prior to and 10 to 12 weeks following abdominal liposuction. The risk factors included insulin action in fat, muscle, and liver tissues, levels of certain circulating blood inflammatory proteins, cholesterol levels, blood pressure, measures of different types of body fat, and other factors. Based on these risk factors, liposuction did not provide any health benefit to either group, even though it decreased the volume of fat beneath the skin of the abdomen by 44 percent in those without diabetes and 28 percent in those with diabetes. In comparing liposuction with other weight-loss treatments which do improve metabolic risk factors associated with heart disease and diabetes—the investigators noted that liposuction removes subcutaneous fat but does not affect energy balance, that is, the balance between calories eaten and calories the body burns. By contrast, conventional diet and exercise decrease fat mass in different locations, including the fat that surrounds body organs, and creates a "negative" energy balance, which results in weight loss. The research indicates that, although liposuction removes substantial amounts of fat from beneath the skin, it alone is not sufficient to protect against obesity-associated diseases. Thus, conventional weight-loss regimens, such as diet and exercise, should be employed for effective improvement of the status of diabetes and coronary heart disease risk factors.

Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW, and Mohammed BS. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med* 350: 2549-2557, 2004.

Intervention Prevents Excessive Weight Gain During Pregnancy in Low Income Women: Excessive gestational weight gain can have deleterious effects on both mother and child, such as complications during pregnancy, increased risk of cesarean delivery, and high infant birth weight. Researchers have tested a two-part intervention for its effect on preventing excessive gestational weight gain. The first part consisted of a clinical component, in which the women's health care providers used new tools (such as a gestational weight gain grid) to provide guidance about monitoring weight gain. In the second part, the women received patient education materials by mail. The researchers tested the intervention on women who were either overweight or normal weight at early pregnancy, and followed them until one-year postpartum. Overall, the intervention did not have any effect on preventing excessive gestational weight gain or preventing weight retention at one-year postpartum. However, when the researchers analyzed a low-income subgroup of women, they observed that the intervention effectively prevented excessive weight gain in both the overweight and normal weight low-income women; it also effectively prevented one-year postpartum weight retention in overweight, low-income women. Previous studies have shown that low-income women are at increased risk for excessive gestational weight gain. Therefore, the researchers have identified a successful intervention for this high-risk group of women.

Olson CM, Strawderman MS, and Reed RG. Efficacy of an intervention to prevent excessive gestational weight gain. *Am J Obstet Gynecol.* 191: 530-536, 2004.

The Molecular Physiology of the Control of Body Weight

Dr. Rudolph Leibel

The NIDDK National Advisory Council meets three times annually to provide advice to the Institute regarding its research portfolio and broad issues of science policy. These meetings are also an opportunity for the Council members to learn about recent scientific advances in different fields through presentations from NIDDK-supported extramural scientists. At one of the meetings in 2004, the Council and NIDDK staff were privileged to hear from Dr. Rudolph Leibel. The "Scientific Presentation" in this chapter is meant to capture the essence of his talk.

Rudolph Leibel, M.D., is Professor of Pediatrics and Medicine and Head of the Division of Molecular Genetics at Columbia University College of Physicians and Surgeons. He is also a member of the Institute of Medicine of the National Academies. A graduate of Colgate University, Dr. Leibel received an M.D. from Albert Einstein College of Medicine. His research focuses on the molecular physiology of the regulation of body weight in rodents and humans, and on the genetics of type 2 diabetes mellitus. Current research activities include efforts to identify genes (and relevant genetic variants) related to obesity and/or type 2 diabetes in mice and humans. Dr. Leibel's laboratory is dedicated to efforts to use basic, clinical, and translational research to understand human disease.

Dr. Leibel emphasized the dramatic recent increase in obesity in the United States, and its serious health consequences. In parallel to the rising rates of obesity, there has been an escalation in the levels of type 2 diabetes, for which obesity is a major risk factor. Other diseases for which obesity is a contributing factor include gallbladder disease, hypertension, and coronary heart disease, and cancer. Extensive research is shedding light on the biological control of body weight; however, finding ways to prevent and treat obesity remains challenging.

Biological Basis for the Control of Body Weight

While there are molecular controls over body weight, the body's innate regulatory defenses against loss of fat are apparently stronger than its defense against weight gain. Why is body weight (fat mass) regulated? With respect to maintaining a specific minimal level of fat, Dr. Leibel offered two answers to this question. First, a certain amount of fat (energy) is required for reproduction, including the ability to carry pregnancy to completion. Second, from an evolutionary perspective, stores of fat would have conferred protection against the environmental vicissitudes faced by our ancestors, in times when food supply was often limited. How is body weight regulated? In substantial part, this regulation is coordinated in the brain. There is a close relationship between these molecular regulatory processes and the behaviors critical to energy balance: energy intake (eating) and energy expenditure.

Numerous genes for hormones and other molecules involved in body weight regulatory pathways have been identified in mice. Scientists have also identified the human counterparts of these mouse genes, helping to elucidate the molecular control of energy balance in humans and also demonstrating the value of animal models in obesity research.

Image courtesy of the Jackson Laboratory.

Over time, a very small, persistent imbalance of energy intake over energy expenditure can lead to substantial weight gain; for example, Dr. Leibel noted that the frequent experience of gaining approximately 30 pounds (15 kg) in about 30 years, as in middle age, reflects only a 3.6 percent excess of energy intake over expenditure. From a research perspective, it will be important to develop tools to measure energy intake and expenditure with sufficient precision and accuracy to identify the nature of such small energy imbalances.

The extraordinarily complex regulatory system that controls body weight converges in a part of the brain called the hypothalamus. The brain receives signals from the blood and other organs and tissues, and it also produces molecules that can affect energy intake and expenditure. For example, the hormone leptin, secreted by fat cells, stimulates brain molecules that lead to reduced food intake, while the hormone ghrelin, produced in the gastrointestinal tract, acts to stimulate brain molecules that help drive food intake. Numerous genes for the hormones and other molecules involved in these body weight regulatory pathways have been identified in mice. Scientists have also identified the human counterparts of these mouse genes, helping to elucidate the molecular control of energy balance in humans and also demonstrating the value of animal models in obesity research. Several rare forms of human obesity result from inactivating mutations in genes that encode components of this regulatory system, including leptin and others, such as a molecule that derives from a protein called proopiomelanocortin (POMC), and the melanocortin 4 receptor, which interacts with one of the POMC-derived molecules.

A rare form of obesity—the Prader-Willi syndrome—results from a different type of genetic abnormality. Scientists have identified a small chromosomal region that is associated with this syndrome, and are working to pinpoint the genes involved. Bardet-Beidl Syndrome, another rare form of obesity, has been associated with eight different genes. A connection among several of these genes—components of a molecular structure on some brain cells—was revealed recently as a result of experiments with the corresponding genes in worms.

More common forms of obesity also have a strong genetic component. Based on studies of twins, scientists estimate that 40 to 60 percent of susceptibility to obesity is attributable to genes. For example, different people gain different amounts of weight when overfed by a specified amount, but identical twins—who share the same genes—gain similar amounts of weight. The genetic bases of common forms of obesity, however, are very complex, and susceptibility is likely influenced by many genes. Numerous regions of the genome have been implicated as containing genes that regulate body weight, and scientists are currently trying to identify these genes. Why should we have all these genes that tend to protect body weight? Genes that promote energy storage were, at one point early in human history, likely beneficial. However, in the current environment of plentiful food, such a genetic makeup leaves one prone to obesity.

Why Is Obesity So Hard To Prevent or Treat?

Dr. Leibel explained that obesity prevention and treatment are difficult not only because of the environment, but also in part because a loss of weight (fat mass) triggers the body to make compensatory adjustments in its energy expenditure that favor weight regain. That is, formerly obese individuals—those who have lost fat mass—actually require fewer calories to maintain their new weight than do individuals of the same weight who were never obese. The consequences of such weight loss, seen in patients, can include not only a slowing of their metabolic rate (energy expenditure), but also decreased satiety, increased hunger, increased work efficiency of skeletal muscles (i.e., the muscles can do more with less energy), a state of infertility, and other metabolic effects. One explanation of this phenomenon is that each individual may have a threshold for the action of leptin—a key hormone produced by fat cells, as noted previously. Each person's threshold is set by subtle sequence variations in his or her genes. When fat mass is decreased by weight loss, insufficient leptin is produced to cross this threshold.

In a clinical study that Dr. Leibel and his colleague Dr. Mike Rosenbaum conducted, individuals who had lost 10 percent of their body weight, an amount sufficient to bring about substantial health benefits, were administered just enough leptin to restore pre-weight-loss levels of the hormone. This extra leptin apparently "tricked" the brain into thinking the fat was still there, as it reversed many of the compensatory changes that normally accompany weight loss, including decreased energy expenditure.

Given these biological factors—genetics, the innate regulatory system for energy balance, and the body's natural compensatory responses to lost weight that promote weight regain—along with the current environment, losing weight, and especially maintaining weight loss are extremely difficult. The health benefits of modest weight loss are quite striking, but current treatment strategies are clearly not ideal, as reflected in very high rates of relapse to obesity.

Future Research Directions

Dr. Leibel concluded with a discussion of future research directions towards obesity prevention and treatment. The continued identification of molecules involved in body weight regulation will be important, as these could serve as new targets for drug development. It will be valuable to assess the effects of public health approaches that reduce the use of calorie-dense foods and increase physical activity. Another area for future study is research on body weight in children, including determining the optimal timing for intervention to prevent or reverse obesity. Various types of genetic approaches will enhance understanding of different forms of obesity, as well as type 2 diabetes. Finally, the development of new molecular diagnostics should help to evaluate susceptibility and to assist in the selection of therapies—which, although limited now, will hopefully be improved with continued research.

Weight-loss Surgery: Assessing Its Role in the Treatment of Obesity

Weight loss can be tough for anyone and for someone who is obese it can be a particularly daunting challenge. Moreover, for people who are extremely obese, expected weight loss from behavior change alone may not be sufficient to have a major impact on health and is unlikely to be sustained. Bariatric surgical procedures, which restrict stomach size and/or lead to decreased absorption of nutrients, are being increasingly performed to treat severe obesity. These procedures can have dramatic benefits—such as sustained weight loss, improved control of blood sugar levels, or even reversal of type 2 diabetes—especially when accompanied by a healthy diet and exercise. However, they also carry substantial risks, including death in a small number of patients.

Despite the increasing popularity of bariatric surgery, crucial questions still remain, such as how best to identify candidates for surgery, and the extent of potential health benefits *versus* potential risks. Researchers would also like to figure out precisely how certain types of bariatric surgery work to help patients maintain weight loss or to improve obesity related diseases. To address many of these questions, the NIDDK is building upon recent advances and emerging opportunities as a foundation for new research efforts—including a major new clinical research initiative.

What Is Bariatric Surgery?

In recent years, bariatric surgery, also called weight-loss surgery, has garnered a lot of media attention. However, the first surgery of this type used for severe obesity actually dates back 40 years and grew out of the results of operations for certain cancers or severe ulcers. Doctors became aware that their patients lost weight following surgeries that removed large portions of the stomach or small intestine. Some physicians began to use such operations to treat patients with severe obesity. Over time, these operations have been modified to improve patient safety and to incorporate technological advances in surgical procedure. Today, there are basically two types of bariatric operations: restrictive and malabsorptive.

In restrictive operations, physicians use surgical staples and/or a special band to create a small pouch at the top of the stomach at the point that food enters from the esophagus. These operations restrict food intake but do not interfere with the normal digestive process. Patients lose the ability to eat large amounts of food at one time. Although restrictive operations lead to some degree of weight loss in almost all patients, these surgeries are less successful in inducing sustained weight loss. This result is largely because patients must still adjust their diets to reduce total caloric intake, and can “out eat” their surgery with frequent small portions of liquid calories or easily absorbed foods.

Malabsorptive operations, on the other hand, restrict both food intake and the amount of calories and nutrients the body absorbs, and are by far the most common gastrointestinal surgeries for weight loss. The most commonly performed operation, which has both a restrictive and malabsorptive component, is the Roux-en-Y Gastric Bypass. These procedures connect the upper stomach to the lower part of the small intestine, so that food bypasses a large portion of the gastrointestinal tract in which digestion and nutrient absorption normally take place. Patients who have this type of surgery generally lose two-thirds of their excess weight within two years, and tend to keep much of it off for years. The tradeoff for patients is a greater risk of developing nutritional deficiencies, especially in iron and calcium. Other malapsorptive procedures, such as the biliopancreatic diversion with or without duodenal switch, produce even more dramatic weight loss, but at the expense of more complications, including nutritional deficiencies.

Who Is Having Bariatric Surgery?

The prevalence of overweight and obesity has risen dramatically in the United States over the past several decades. Even more alarmingly, the prevalence of extreme obesity has risen at a faster pace. One widely used measure of excess weight is the body mass index (BMI), a ratio of a person's weight in kilograms divided by the square of his or her height in meters. Between the period 1988 to 1994 and the period 1999 to 2000, the age-adjusted prevalence of obesity among adults in the nation, as measured by BMI, rose from 55.9 to 64.5 percent; however, the prevalence of extreme obesity—a BMI of 40 or more—rose in the same period from 2.9 to 4.7 percent.

The trend of increased obesity in the U.S. population has been paralleled by an increase in the number of bariatric surgeries performed: According to the American Society for Bariatric Surgery, the number of operations increased from about 16,000 in the early 1990s to more than 103,000 in 2003.

The popularity of bariatric surgery arises from its ability to overcome the major challenges of treating extreme obesity: bariatric surgery is currently the most effective means to induce substantial weight loss and to maintain that loss. However, bariatric surgery is not a cosmetic procedure, but a major, serious operation requiring lifelong adjustments in diet and behavior to ensure success. Moreover, adults who are candidates for these procedures are usually not in the best of health. They have a BMI of 40 or more—the equivalent of 80 to 100 pounds or more of excess weight—or a BMI of 35 or more and serious obesity-related complications, such as cardiopulmonary problems, type 2 diabetes, severe sleep apnea, or joint problems. These conditions place bariatric surgery candidates at high risk for death or complications, either from their obesity-related medical problems, or from the surgery itself. Thus, the benefits and risks of bariatric surgery need to be carefully assessed before an already vulnerable patient embarks on this challenging course of treatment for obesity and its complications.

KNOWN BENEFITS AND RISKS OF BARIATRIC SURGERY

Benefits of Bariatric Surgery

- Bariatric surgery generally leads to weight loss, with results varying depending upon the type of surgery selected. For example, between 18 to 24 months after malapsorptive surgery most people lose two-thirds of their excess weight, much of which is sustained over many years.
- Bariatric surgery leading to weight loss improves most obesity-related conditions, including diabetes, high blood pressure, lipid abnormalities, and sleep apnea.

Risks of Bariatric Surgery

- 10 to 20 percent of patients require follow-up operations to correct complications, most commonly abdominal hernias.
- Some patients develop gallstones, which are clumps of cholesterol and other matter that form in the gallbladder. However, taking supplemental bile salts can prevent gallstones from developing.
- Nearly 30 percent of patients develop nutritional deficiencies such as anemia, osteoporosis, and metabolic bone disease, which can be avoided by taking sufficient amounts of vitamins and minerals.
- Women of childbearing age should avoid pregnancy until their weight becomes stable, because rapid weight loss and nutritional deficiencies can harm a developing fetus.
- Some patients experience psychological difficulties.
- Estimates of postoperative death rates for bariatric surgery patients range from 0.1 to 2 percent.

Longitudinal Assessment of Bariatric Surgery (LABS)

While bariatric surgical procedures can have dramatic health benefits, they also carry substantial risks, including death. Thus, it is very important for physicians and potential patients to have the most comprehensive information possible with which to make well-informed choices about weight-loss surgery as a means to treat extreme obesity. Until recently, this information has been limited by a paucity of systematic research that could help determine the full spectrum of risks and benefits and provide evidence-based guidance on appropriate patient selection. In particular, researchers have lacked a common database of information on patients and outcomes for healthcare professionals.

Responding to this information gap, the NIDDK has been working to advance efforts to examine bariatric surgery more carefully as a treatment option for obesity. In 2001 and 2002, the NIDDK convened groups of external experts to discuss recent developments in bariatric surgery, to identify pressing clinical questions, and to identify scientific research opportunities pertaining to bariatric surgery and its impact on obesity and co-morbid conditions. These meetings built upon earlier findings from a 1991 NIH Consensus Development Conference on bariatric surgery. The first meeting, a workshop convened in collaboration with the American Society for Bariatric Surgery, focused on clinical research issues. The workshop participants emphasized the need to determine the impact of bariatric surgery on subsequent pregnancy, the impact of age on outcomes, and the effect of operations with greater malabsorptive potential on nutritional status.

In May 2002, this effort was expanded by the NIDDK Working Group on Bariatric Surgery. Through a two-day meeting, the group identified numerous clinical and basic research opportunities related to bariatric surgery, such as using this surgery as a model to understand the underlying pathophysiology of obesity-related diseases—many of which are reversed or ameliorated following surgery. Another research opportunity is the evaluation of the safety and efficacy of bariatric surgical procedures, including their impact on weight loss, obesity-related health conditions, psychosocial status, quality-of-life, and economic factors. Studies looking at both short-term and long-term outcomes for patients were felt to be critical. Also considered essential is the refinement of the evaluation of factors that may contribute to a person's obesity (such as physiologic, metabolic, and genetic factors) to better predict outcomes, and hence improve the ability to assess the risk/benefit ratio for an individual bariatric surgery patient. The development of a patient database was recommended.

Based upon the input from external experts, the NIDDK has now established a bariatric surgery clinical research consortium, the Longitudinal Assessment of Bariatric Surgery (LABS), to facilitate and accelerate research in this area. Over the course of five years, the LABS consortium will plan, develop, and conduct coordinated clinical, epidemiological, and behavioral research in bariatric surgery, both restrictive and malabsorptive operations. This consortium will help pool the necessary clinical expertise and administrative resources to facilitate the conduct of multiple and novel clinical studies in a timely, efficient manner. Development of a database using standardized definitions, clinical protocols, and data collection instruments will enhance the ability to provide meaningful evidence-based recommendations for patient evaluation, selection, and follow-up care. This database, in turn, will promote rapid dissemination of research findings to healthcare professionals.

In addition, this consortium will serve as a resource for basic and clinical studies to explore the mechanisms by which bariatric surgery affects obesity-related health conditions, physical activity, appetite and eating behaviors, and psychosocial factors. This research may lead to improved understanding of the factors underlying the development of obesity, with implications for new strategies for prevention and treatment. For example, recent studies suggest that malabsorptive bariatric surgeries disrupt normal neural, gastrointestinal, and endocrine pathways that influence appetite, physical activity, and the sense of fullness. Researchers hypothesize that these disruptions may explain, in part, the success of malabsorptive operations in the maintenance of weight loss. Thus, studies of large numbers of persons

who have undergone bariatric surgery may also provide new insights into the role of peripheral signaling (signaling from various parts of the body to the control centers in the brain) in controlling the balance between energy intake (calories) and energy expenditure (physical activity and metabolism) that is derailed in obesity. New NIDDK-led initiatives are encouraging such research, to be performed as ancillary studies to the LABS consortium.

Enrollment for the LABS consortium is expected to begin in early- to mid-2005. Through the LABS and related research efforts, the NIDDK hopes to improve the understanding and application of bariatric surgery as a treatment for severe obesity. Although prevention remains the primary public health goal in the face of rising rates of overweight and obesity, more effective treatments are crucial for those who are already obese. Studies on bariatric surgery will likely contribute to both these objectives.

Weighing In On Weight-Loss Surgery—One Patient's Perspective

By age 43, biologist Eli Ney, at 242 pounds, was overweight by well over 100 pounds, which classified her as morbidly obese. Eli, now 45, says that over the years she had been on every type of diet imaginable, and that, on at least two occasions, she had lost 100 pounds or more, only to put them back on. "After a while the dieting became very discouraging," she says. However, two years after undergoing bariatric surgery, Eli now maintains her weight at 128 pounds—"give or take a pound or two," she chuckles. Through good eating habits and continued exercise, she intends to keep it that way. But, Eli admonishes that anybody contemplating weight-loss surgery needs to do their homework. "You had better know what you're getting yourself into before you get on that operating table," she says.

The Surgery: Eli never had it easy when it came to controlling her weight. "I've always been on a diet, even when I was a child," she says. As a very little girl she remembers always having "a pooch around my middle." Eli's family also has a health history that includes type 2 diabetes, which is often associated

Eli Ney

with being overweight. "My mother has type 2 diabetes, high blood pressure, high cholesterol, and abdominal obesity. Several years ago she had a heart attack. I saw myself heading down that path," she says.

At age 42, in lieu of attempting yet another frustrating diet, Eli decided to research the pros and cons of bariatric surgery. She decided that, for her, the potential positive outcomes were worth the known risks. In August 2001, she submitted health information to a bariatric physician—including her dieting history, current weight, and BMI. In May of 2002, she had Roux-en-Y bypass surgery, the most common form of malabsorptive surgery. The surgery initially reduced her stomach capacity from three pints to one ounce of food, a tremendous adjustment in terms of food intake. Any overeating whatsoever now can cause "dumping syndrome," which means that the contents in Eli's stomach move too rapidly through her small intestine. Symptoms include nausea, weakness, sweating, faintness, and sometimes diarrhea after eating, and it can "knock you out for hours," says Eli.

The first day or two after surgery, Eli found it difficult to get up and walk, but within 2½ weeks she was back at work. "People ask me all the time 'Do you feel different?,' but I don't, really," she says. Eli is outgoing—she has been a member of a Toast Masters speakers' club since 1998—and always has had a strong self-image. But she does acknowledge that, once she started losing weight, people began paying more attention to her. "Weight-loss can be a pretty intense experience, especially when you realize how differently you are treated," says Eli. "Some

people who wouldn't even say 'hi' to me before, do now. It's sad but true."

Benefits: Within 18 months of her surgery, Eli arrived at her current 128 pounds. The surgery also reduced most of the other obesity-related conditions she had been experiencing—including high blood sugar levels, a warning sign of impending type 2 diabetes. For Eli, however, the real test of the surgery's success came during times of personal crisis that followed closely on the heels of her operation. "As a result of my surgery, I felt empowered not to use food as a coping mechanism," she says.

Side Effects: In addition to "dumping syndrome," Eli has experienced a number of side effects from the surgery, due to the reduced absorption of nutrients. For example, Eli says she lost 25 percent of her hair because of protein loss. "It's all back now, but it's scary when you're combing your hair and large hanks of it come out in the brush." Also, since the surgery, Eli has gone from being 5-feet 3½ inches tall to 5-feet 2¾ inches. She attributes this to bone loss and osteoporosis and is careful about making sure she gets her daily supplements of calcium. As a result of the surgery, she also has mild anemia, which she counteracts with iron supplement pills, on top of a regimen that includes daily doses of multiple vitamins and a shot of B12 supplement every 6 months. Eli recently underwent reconstructive surgery to remove excess skin caused by the loss of such a large amount of weight. "For some people reconstructive surgery is mandatory. For me it was optional, but it was something I felt I needed to do to complete this process."

To this day, Eli is committed to good diet and to avoiding foods that contain sugar, including cookies, cakes or sweetened soft drinks, as well as breads and other foods high in carbohydrates. She also continues to exercise regularly. In fact, Eli is so committed to her new life that she is currently using her Toast Master speaking skills to reach out to obese men and women to explain to them their options for losing weight, and is considering writing a book about her own experience. "I've already got a title," Eli says cheerily. "Extreme Makeover from the Inside Out."

WIN: NIDDK's Weight-control Information Network

The NIDDK's Weight-control Information Network (WIN), provides the general public, health professionals, and the public with up-to-date, science-based information on obesity, weight control, physical activity, and related nutritional issues. This information includes fact sheets and brochures for the public, as well as *WIN Notes*, a periodic newsletter for health professionals and consumers. Through its information services, WIN reaches out to people of all ages, and to diverse ethnic and racial groups.

WIN is conducting several outreach activities. Among these is an ongoing project to promote the distribution by healthcare providers, including primary care providers, of information regarding food labels, regular physical activity, and how to help obese patients. Another outreach effort to community health clinics focuses on WIN's series of booklets on "Cómo Alimentarse y Mantenerse Activo Durante Toda La Vida" ("Healthy Eating and Physical Activity Across Your Life Span"). This project involves communications to physicians, dietitians, and community health centers, including Hispanic healthcare professionals and community healthcare centers that serve predominantly Hispanic populations. The "Toda La Vida" series of booklets, available in English and Spanish, contains booklets targeted to different populations, including "tips for adults," "tips for older adults," "tips for parents," and "tips for pregnancy."

WIN's "Sisters Together: Move More, Eat Better" is a national initiative that encourages African American women to maintain a healthy weight by becoming more physically active and eating more healthful foods. Among its publications are: "Celebrate the Beauty of Youth!," which was published this past year, "Fit and Fabulous as You Mature," "Energize Yourself and Your Family," and "Walking...A Step in the Right Direction." WIN is conducting an outreach effort to contact historically Black colleges and universities (HBCUs) and various community venues to promote the availability of "Sisters Together" brochures.

This past year, WIN redesigned its Website with the goal of making information regarding weight loss and control easier to find and navigate. The new address is *http://win.niddk.nih.gov*.